Associations of early systolic blood pressure control and outcome after thrombolysis-eligible acute ischemic stroke: results from the ENhanced Control of Hypertension ANd Thrombolysis stroke study (ENCHANTED)

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Abstract

Background and Purpose: In thrombolysis-eligible patients with acute ischemic stroke (AIS), there is uncertainty over the most appropriate systolic blood pressure (SBP) lowering profile that provides an optimal balance of potential benefit (functional recovery) and harm (intracranial hemorrhage [ICH]). We aimed to determine relationships of SBP parameters and outcomes in thrombolyzed AIS patients.

Methods: Post-hoc analyzes of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), a partial-factorial trial of thrombolysis-eligible and treated AIS patients with high SBP (150-180 mmHg) assigned to low-dose (0.6mg/kg) or standard-dose (0.9mg/kg) alteplase and/or intensive (target SBP 130-140 mmHg) or guideline-recommended (target SBP <180 mmHg) treatment. All patients were followed up for functional status and serious adverse events to 90 days. Logistic regression models were used to analyze three SBP summary measures post-randomization: *'attained'* (mean), *'variability'* (standard deviation) in 1-24 hours, and *'magnitude'* of reduction in 1 hour. The primary outcome was a favorable shift on the modified Rankin scale (mRS). The key safety outcome was any intracranial hemorrhage (ICH).

Results: Among 4,511 included participants (mean age 67 years, 38% female, 65% Asian) lower attained SBP and smaller SBP variability were associated with favorable shift on the mRS (per 10 mmHg increase: odds ratio [OR] 0.76, 95% confidence interval [CI] 0.71–0.82, p<0.001 and 0.86, 95% CI 0.76-0.98, p=0.025) respectively, but not for magnitude of SBP reduction (0.98, 0.93-1.04, p=0.564). Odds of ICH was associated with higher attained SBP and greater SBP variability (1.18, 1.06-1.31, p=0.002 and 1.34, 1.11-1.62, p=0.002), but not with magnitude of SBP reduction (1.05, 0.98-1.14, p=0.184).

Conclusions: Attaining early and consistent low levels in SBP <140 mmHg, even as low as 110-120 mmHg, over 24 hours is associated with better outcomes in thrombolyzed AIS patients.

Clinical Trial Registration Information: The trial is registered at ClinicalTrials.gov (NCT01422616).

Introduction

Intravenous (iv) thrombolysis treatment with recombinant tissue plasminogen activator (rtPA/alteplase) is a proven effective medical therapy in acute ischemic stroke (AIS). Although co-morbid elevated blood pressure (BP) is common after AIS,[1] often to extreme levels, and is associated with poor outcomes,[2] there is controversy over the benefits of peri-thrombolysis BP control, where guidelines consistently recommend an SBP <185mmHg[3, 4] in thrombolyzed AIS patients. However, the recently completed BP arm of the quasi-factorial Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) suggests an even lower target may further improve outcomes in this patient group. In thrombolysis-eligible and treated AIS patients with elevated SBP (150-180 mmHg), intensive BP control (target SBP 130-140 mmHg within 1 hr) was not shown to improve clinical recovery as compared to standard (SBP <180 mmHg) BP lowering over 72 hours,[5-9] but the treatment did lead to significant reductions in the key safety outcome of intracranial hemorrhage (ICH), and in particular large intracerebral hemorrhage.[8]

Among the various measures used to define SBP control,[10-14] studies have shown that higher mean,[15-17] greater variability,[18-20] and smaller reductions[19, 20] in post-thrombolysis SBP are associated with higher odds of ICH[15, 17-20] and worse functional outcome from AIS.[17-20] However, such observational analyzes may be complicated by residual confounding and incomplete assessment of interactions between variables, the optimal level of SBP control for functional recovery and risk of ICH without worsening cerebral ischemia is unknown. Therefore, we undertook post-hoc analyzes of the completed ENCHANTED dataset of both the combined alteplase-dose[6, 7, 9] and BP arms[5, 8] to determine associations of summary measures - *'attained'* (mean) and *'variability'* (standard deviation) during 1-24 hours, and *'magnitude'* of reduction in 1 hour- of early SBP control, and key clinical outcomes. The aim was to determine the strength and direction of associations, explore any effect modification by patient

characteristics, and identify a SBP lowering profile that provided an optimal balance of potential benefit (functional independence) and harm (ICH and serious adverse events [SAE]).

Methods

Study design population

Details of the study design and main results of the BP and alteplase dose arms of the ENCHANTED trial have been detailed elsewhere. [5-9] In brief, ENCHANTED was an international, 2x2 partial-factorial, multi-center, prospective, randomized, open-label, blinded-endpoint (PROBE) trial. All ENCHANTED adult (age ≥18 years) participants had a clinical diagnosis of AIS confirmed by brain imaging and fulfilled local criteria for thrombolysis treatment. The alteplase-dose evaluation arm[7] was conducted from March 1, 2012 to August 31, 2015, and included a total of 3310 participants randomly assigned to receive low-dose (0.6 mg/kg; 15% as bolus and 85% as infusion over 1 hour) or standard-dose (0.9mg/kg; 10% as bolus and 90% as infusion over 1 hour) intravenous alteplase. The BP arm[8] was conducted from March 3, 2012 to April 30, 2018, and included a total 2227 participants with elevated SBP (150-180 mmHg) where the attending clinician had uncertainty over the benefits and risks of the intensity of BP control, immediately and for 72 hours (or hospital discharge or death if this occurred earlier) after thrombolytic treatment. Although there was no specified upper SBP level, international guidelines recommend patients have SBP ≤185 mmHg prior to administration of intravenous alteplase.[3] Participants were randomly assigned to a strategy of intensive BP lowering (target SBP 130-140 mmHg within 60 minutes of randomization) or guideline-recommended BP lowering (target SBP <180 mmHg) after the commencement of intravenous alteplase.

Procedures

The management strategy of BP lowering treatment was according to local protocols based upon available intravenous (bolus and infusion), oral and topical medications.[8] All patients were to be managed in an acute stroke unit, or an alternative environment with appropriate staffing and monitoring, and receive active care and best practice management according to local guidelines. The use of endovascular thrombectomy was allowed, but was uncommon during the course of the trial.

Non-invasive BP monitoring was undertaken using an automated device applied to the non-hemiparetic arm (or right arm in situations of coma or tetraparesis) with the patient resting supine for $\geq$3 minutes according to a standard protocol. Following thrombolysis, BP measurements were recorded every 15 minutes for 1 hour, and 6-hourly from 1 to 24 hours. Thereafter, BP was recorded twice daily for one week (or until hospital discharge or death, if earlier). Neurological status, according to the National Institutes of Health Stroke Scale (NIHSS) and Glasgow coma scale (GCS), was assessed at baseline, 24 and 72 hours, and 7 days. Brain imaging (computerized tomography and/or magnetic resonance imaging) was conducted at baseline, and 24 hours, and additionally if clinically indicated, analyzes were undertaken centrally for diagnoses of categories of ICH by expert assessors who were blind to clinical details and treatment allocation. Socio-demographic and clinical details were obtained at randomization, while follow-up data were collected at 24 and 72 hours, seven days (or at hospital discharge if earlier), and 28 and 90 days.

For each participant, summary measures of SBP control were: *'attained SBP'*: the mean of five time-points of SBP measures between 1 and 24 hours; '*variability of SBP'*: the standard deviation (SD) of the same measures between 1 and 24 hours; and '*magnitude of early reduction of SBP'*: the difference between randomization SBP and the lowest attained SBP within the first hour. For sensitivity analysis, the latter measure was further defined as *'magnitude of later reduction of SBP':* the difference between SBP at randomization and the lowest attained level

within the first 24 hours. Linear interpolation (PROC TRANSREG in SAS) were used to estimate missing SBP measurements at defined time-points, and regression functions with 3-knot splines were fitted to allow enough change points to capture the projected turn of SBP trajectory without undue overestimation.[21]

Outcomes

For these analyzes, the primary outcome was functional status as defined by the distribution of scores on the modified Rankin scale (mRS). Secondary outcomes were: any ICH reported by investigators with or without central adjudication of relevant brain imaging within seven days after randomization; mRS scores 0-1; mRS scores 0-2; and death within 90 days. Safety outcomes were: death or neurological deterioration, defined as an increase from baseline of ≥4 points on the NIHSS or a decrease from baseline of ≥2 points on the GCS, within seven days; and any fatal or non-fatal SAE according to standard definition.

Data analysis

The relationships of early SBP control parameters and death or disability were first explored using the locally-estimated scatterplot smoothing (LOESS) procedure. When this suggested a potential non-linear relationship (quadratic or cubic), either a squared (X^2) or cubed (X^3) term was added to the regression model, respectively. Next, interaction effects (attained x magnitude, variability x magnitude, attained x variability, and magnitude x attained x variability) were assessed; if there was no significant interaction, a reduced model was run without an interaction term. For all the analyses involving the primary outcome of functional status (ordinal shift in the distribution of scores on the mRS), we first checked that the proportional odds assumption, and if it was violated, we used secondary outcome of mRS 0-1.

For each outcome, the primary model included all three summary measures of SBP control as continuous variables, where associations are reported as odds ratios (OR) with 95% confidence

intervals (CI) per 10 mmHg SBP increase. The following baseline variables were included in multivariable analyzes: age, sex, ethnicity (Asian vs. non-Asian), degree of neurological impairment (NIHSS score), pre-morbid function (mRS scores 0 vs. 1), pre-morbid use of antithrombotic agents (aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase). Next, the individual SBP summary measures were assessed as categorical variables for descriptive purposes, and reported as comparisons between each category and the reference category as OR with 95%CI. To determine any potential modifying effects, interaction terms with baseline covariates were added to the primary model. For any covariate that yielded a significant interaction effect, a subgroup analysis was conducted. Sensitivity analyzes using complete case data and BP control parameters from 2 to 7 days were also conducted.

Finally, a machine learning Stochastic Gradient boosting algorithm (with Gaussian distribution and applying 5000 trees)[22] was executed to estimate the relative influence of the three summary measures of SBP control and the covariables listed previously to assess their importance in explaining the variability of the outcomes of interest. The percentage relative influence was computed using an empirical-permutation procedure that evaluates the average decrease in accuracy across all the constructed trees (the largest the decrease, the more important the variable).

All analyzes were undertaken using SAS (version 9.2 or newer) and the GBM package in R. Statistical significance was set at two sided $p < 0.05$ throughout.

Role of the funding source

The sponsors and funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all study data and share responsibility for the decision to submit the paper for publication.

Results

A total of 4,511 ENCHANTED participants (mean age 67 years, female 37.9%, Asian ethnicity 65.4%) were included in these analyzes (figure SI, table I). The median time from onset of symptoms to randomization (intensive vs. guideline-recommended BP lowering treatment) was 2.9 hours (interquartile interval [IQI] 2.2 to 3.7). Other key baseline characteristics and details of study treatment, including alteplase dose and BP lowering, are provided in Table I. On average, the magnitude of SBP reduction in the first one and 24-hour post-randomization periods were 16 (17) and 30 (18) mmHg, respectively; and attained level and variability of SBP were 139 (15.3) mmHg and 12 (6.5) mmHg, respectively, over 1 to 24 hours. There were 916 patients who participated in both randomized treatment arms (low-dose vs. standard-dose alteplase and intensive vs. guideline-recommended BP lowering treatment); 2326 and 1269 were randomized only to the alteplase dose and BP arms, respectively. SBP data were imputed for 1416 patients; 3095 patients had no imputation (42 without any SBP data, 149 died early, and 2904 with complete records).

As the LOESS plot suggested a potential U-shaped relationship between magnitude and death or disability (figure SII), a squared (X^2) term was added to the regression model but was subsequently removed as it was not significant. All interaction terms were also not significant and thus also excluded from models. The proportional odds assumption was not rejected (p=0.250). Table II shows associations of the three SBP summary measures as continuous variables in a combined adjusted model. There were significant linear associations with functional status for attained level and variability of SBP: ORs were 0.84 (95% CI 0.81 to 0.87;

p<0.0001) and 0.88 (95% CI 0.81 to 0.96; p=0.004) per 10 mmHg increase, respectively. However, there was no association for magnitude (OR 1.00, 95% CI 0.97-1.04; p=0.969). Similar significant/non-significant associations were observed for the SBP parameters and the other outcomes.

When the magnitude of SBP reduction was examined over 24 hours, significant linear associations were also seen for attained level and variability of SBP: OR were 0.85 (95% CI 0.82 to 0.89; p<0.0001) and 0.84 (95% CI 0.76 to 0.93; p=0.028) per 10 mmHg increase, respectively. Attained SBP was significantly associated with mRS scores 0-1 (0.81, 0.77-0.85, p<0.0001); death or neurologic deterioration within 7 days (1.25, 1.16 to 1.33, p<0.0001), but not for any ICH, death, and any SAE.(table II). There were significant linear associations between SBP variability and all the other outcomes: adjusted OR per 10 mmHg SBP increase for mRS scores 0-2 (0.85, 0.76-0.95, p=0.004); any ICH (1.22, 1.08 to 1.37, p=0.002); death or neurologic deterioration within 7 days (1.35, 1.18 to 1.54, p<0.01); death (1.32, 1.130 to 1.55, p=0.001); and SAE (1.37, 1.23 to 1.54, p<0.0001).

Assessment of the SBP summary measures as categories produced some variation in the shape and significance of associations with outcomes (figure I, tables SI). The general pattern was for lower categories of attained SBP to be associated with greater odds of favorable outcomes. However, a significant linear trend existed for functional status, whereby attained SBP levels of 110-120 mm Hg were associated with the lowest odds of the favorable outcome. For variability, there were significantly positive linear trends across categories with unfavorable outcomes, except for ICH. No significant associations were apparent with the increasing magnitude of SBP reduction.

The associations of SBP summary measures and functional outcomes were consistent in sensitivity analyzes using complete case data (table SII) and BP control parameters from 2 to 7 days (table SIII). There were significant interactions between history of hypertension [p=0.007

for interaction] and SBP summary measures with functional status (table SIV). For patients with a history of hypertension, every 10 mmHg increase in attained and variability of SBP were associated with ~25% increased odds of unfavorable functional status. The association of the variability of SBP reduction and functional status was attenuated, and not significant in patients with history of hypertension (table SV).

Table SVI shows that the three SBP summary measures had equal importance on associations with outcomes: relative influence of attained, variability, and magnitude on ordinal analysis of the mRS (12.74, 14.66, and 13.66, respectively) and any ICH (16.39, 18.97, and 19.26, respectively).

Discussion

In these post-hoc secondary analyzes of SBP data from 4,511 thrombolyzed AIS participants of the ENCHANTED trial, we have shown continuous associations between SBP levels over 24 hours and clinical outcomes. Specifically, for every 10 mmHg of SBP reduction down to as low as 110-120 mmHg early after symptom onset, there was a ~20% reduction in the odds of unfavorable functional status, and separately, greater SBP variability over 24 hours was similarly related to poor functional outcome and ICH.

There have been several lines of investigation over optimal SBP in thrombolysed AIS patients,[15-17] with higher mean levels, greater variability, and a more modest reduction in SBP being associated with unfavorable outcomes. However, these studies may not have fully accounted for confounders and interactions between variables. Our analyzes, therefore, extend such data in providing new observation on the prognostic significance of early SBP control in AIS. Using continuous data, our finding of higher attained SBP and unfavorable outcomes in AIS supports results of the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR),[17] where U-shaped relations of functional outcome

and death centered around a nadir SBP of 141-150 mmHg for optimal favorable outcome was evident. Our analyzes showed more skewed, J-shaped relationships for adverse outcomes, with a nadir as low as 110-120 mmHg, which is much lower than the guideline recommendation of SBP <180 mmHg. Although an excess in mortality for hospitalized AIS patients has been shown for SBP levels of <100 mmHg and SBP <120 mmHg on admission and discharge, respectively,[23] we did not find any clear safety concerns from SBP lowering to these levels in our analyzes, and provides some reassurance over genuine concerns of harm from such treatment promoting cerebral ischemia in the vulnerable penumbral region in AIS. The rationale is that high systemic BP is required to maintain penumbral blood flow from altered cerebral autoregulation in AIS,[24, 25] and that elevated BP is reactive and naturally declines in most cases over several days.[26] Yet, data are accumulating showing not significant hypoperfusion from intensive BP lowering in those with altered cerebral perfusion thresholds and impaired cerebral autoregulation.[27]

Our analyzes also provide support for a prior meta-analysis[28] showing a link between greater SBP variability and poor functional outcome being extended to include a broad range of adverse outcomes including ICH. It is plausible that large fluctuations in SBP may stress the endothelium of cerebral vessels of the ischemic brain and trigger hemorrhage. Furthermore, we provide further support for previous analyzes showing that a lower SBP is associated with a reduced risk of death and disability, such as in the third International Stroke Trial (IST-3) where a modest decline in SBP (10-20 mmHg) from use of any BP treatment within 24 hours of symptom onset was associated with reduced risk of unfavorable outcome, irrespective of the type of agents used.[19] Conversely, the Thrombolysis Implementation and Monitor of acute ischemic stroke in China (TIMS-China) study showed that a substantial decrease (>25 mmHg), compared with a moderate decrease (12-24 mmHg), in SBP over 24 hours was significantly associated with a better outcome;[20] although either a large increase (>25 mmHg) or no change

in SBP was also significantly associated with ICH as compared with a small decrease (1-9 mmHg) in SBP.

Strengths of our study include the large and international dataset, where the high component of vascular comorbidity was highlighted with some two-thirds of AIS patients having a history of hypertension and nearly half taking antihypertensive medication. The pragmatic design and practice-mirroring frequency of BP measurements with analyzes that sort to provide a comprehensive assessment of SBP change in the context of multiple confounders provides some reassurance over the generalizability of the findings to real-world clinical practice. Weaknesses include the important point that we have used the ENCHANTED trial as a cohort study, and many of the observed BP changes were NOT as a result of a randomized comparison. Therefore, despite our efforts to determine the independent significance, ranking, and shape of associations of key early SBP control summary measures, we cannot presume causality in such observational analyzes, and such multiple post-hoc testing raises the potential for chance associations. The BP Arm of ENCHANTED did not show any treatment effect on the standard primary functional outcome, possibly due to only modest SBP differences being attained between randomized groups in a patient group with predominantly mild-moderate neurological impairment. We conducted regression imputation, so the variability of the imputed data might be underestimated. Uncertainty persists over the balance of benefits and risks of intensive BP lowering in patient subgroups, in particular for those eligible for modern endovascular thrombectomy for treatment of large vessel occlusive AIS, and in patients with carotid stenosis.

In summary, we have shown that early rapid and sustained SBP reduction to levels below140 mmHg over 24 hours are associated with more favorable outcomes after thrombolysis for AIS.

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CSA, JC, RIL, TGR and YH conceived the trial. CSA was the chief investigator. CSA, RIL, XC, JC, TGR, ACD were responsible for the day-to-day running of the trial. RIL led the adjudication of neuroimaging and serious adverse events. XW did the statistical analysis with supervision from GLDT. XW, JM, and TM wrote the first draft of the manuscript; all authors revised this draft. All authors read and approved the final version.

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Declaration of interests

GLDT was an Amgen employee until February 2019 and received honoraria for methodological support until December 2020; ; HY RIL and HA has received lecture fees from Bayer, Daiichi-Sankya, Fukuda Denshi, Takeda and Jeijun, and personal fees from Kyowa-Kirin; SL has received personal fees and consultation fees from SANOFI; PMB JPB have received grant

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Supplemental File

Table SI Associations of categorical BP parameters (attained and variability of 1-24h, and magnitude in 1 hour) on outcomes

Table SII Associations of continuous BP parameters on the outcomes using complete data

Table SIII Associations of continuous BP parameters (day 2-7) on the outcomes using complete data

Table SIV Test modification for the association of continuous BP parameters on favorable shift on the ordinal mRS scores at 90 days

Table SV Associations of continuous BP parameters on favorable shift on ordinal mRS score at 90 days by history of hypertension

Table SVI Relative influence of three SBP summary measures on the outcomes, adjusting for baseline characteristics

Figure SI Flow chart of the included patients

Figure SII LOESS plot for associations between blood pressure control parameters and ordinal modified Rankin scale scores

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Figure I Associations of categorical SBP summary measures and outcomes

Figure legend
SBP denotes systolic blood pressure; OR odds ratio; CI confidence interval; ICH intracranial hemorrhage; SAE serious adverse event
*Any intracranial hemorrhage within 7 days
†Death or neurologic deterioration defined as an increase of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) or a decline of ≥2 on the Glasgow coma scale within 7 days post-randomization.
‡Any serious adverse event within 90 days
OR and 95% CI are comparisons between each category and the reference, adjusted for age (<65 vs. ≥65), sex, ethnicity (Asian vs. non-Asian), degree of neurological impairment (NIHSS score <8 vs. ≥8), pre-morbid function (modified Rankin scale scores 0 vs. 1), pre-morbid use of antithrombotic agents (aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

Table I Baseline characteristics, early systolic blood pressure control, other treatments, and outcomes

Variable	
Demographic	
Age (yr)	67 (12.7)
Female sex	1714/4511 (37.9)
Asian ethnicity	2948/4510 (65.4)
Clinical features	
SBP at randomization (mmHg)	154 (18.8)
DBP at randomization (mmHg)	86 (12.7)
Heart rate, beats per minute	79 (15.4)
NIHSS score	8 (5-13)
GCS	15 (14-15)
Medical History	
Hypertension	2916/4508 (64.7)
Stroke	816/4511 (18.1)
Acute coronary syndrome	637/4508 (14.1)
Diabetes mellitus	917/4508 (20.3)
Atrial fibrillation	804/4504 (17.9)
Estimated pre-morbid function (mRS)	
No symptoms (score 0)	3748/4505 (83.2)
Symptoms without any disability (score 1)	757/4505 (16.8)
Medication at time of admission	
Antihypertensive drug(s)	2060/4508 (45.7)
Antithrombotic drug(s)	1064/4505 (23.6)
Presumed stroke etiology	
Large artery disease due to significant atheroma	1796/4463 (40.2)
Small vessel disease	1056/4463 (17.9)
Cardioembolic	797/4463 (17.9)
Early SBP control	
Time from stroke onset to randomization (hr)	2.9 (2.2-3.7)
Attained SBP (mmHg)*	139 (15.3)
SBP variability (mmHg)†	12 (6.5)
Magnitude of SBP reduction in the first hour (mmHg)‡	16 (17)
Magnitude of SBP reduction in the 24 hours (mmHg)#	30 (18)
Randomized treatment	
Low-dose alteplase	1175/4511 (26.1)
Standard-dose alteplase	1151/4511 (25.5)
Standard-dose alteplase/standard BP management	240/4511 (5.3)
Standard-dose alteplase/early intensive BP management	221/4511 (4.9)
Low-dose alteplase/standard BP management	233/4511 (5.2)
Low-dose alteplase/early intensive BP management	222/4511 (4.9)
Standard BP management	638/4511 (14.1)
Early intensive BP management	631/4511 (14.0)
Outcomes	
MRS scores at 90 days	/4431
0	1146 (25.9)
1	1072 (24.2)

2	639 (14.4)
3	521 (11.8)
4	417 (9.4)
5	235 (5.3)
6	401 (9.1)
Any intracranial hemorrhage within 7 days	836/4511 (18.5)
Death or neurologic deterioration§ within 7 days	401/4511 (8.9)
Death within 90 days	557/4511 (12.4)
Any serious adverse event within 90 days	1095/4511 (24.3)

Data are numbers/denominator (%), mean (standard deviation), or median (IQI).
BP denotes blood pressure, DBP diastolic blood pressure, SBP systolic blood pressure, NIHSS National Institute of Health Stroke Scale, GCS Glasgow coma scale, mRS modified Rankin scale

*Mean SBP in 1-24 hours; †Standard deviation of SBP in 1-24 hours; ‡SBP at randomization minus minimum SBP within the first hour; #SBP at randomization minus minimum SBP within the first 24 hours

§Neurologic deterioration defined as an increase of ≥4 points on the NIHSS or a decline of ≥2 on the Glasgow Coma Scale within 24 hr post-randomization.

Table II. Associations of early systolic blood pressure levels and outcomes

Individual SBP summary measures	OR† (95%CI)	p value	OR† (95%CI)	p value
	Attained mean SBP 1-24 hours		**Attained** mean SBP 1-24 hours	
Favorable shift on the mRS score at 90 days	0.84 (0.81-0.87)	**<0.0001**	0.85(0.82-0.89)	**<0.0001**
MRS score 0-1 at 90 days	0.81 (0.77-0.85)	**<0.0001**	0.83(0.78-0.87)	**<0.0001**
MRS score 0-2 at 90 days	0.83 (0.79-0.88)	**<0.0001**	0.85(0.81-0.90)	**<0.0001**
Any intracranial hemorrhage within 7 days	1.04 (0.98-1.10)	0.187	1.04(0.98-1.10)	0.242
Death or neurologic deterioration§ within 7 days	1.25 (1.16-1.33)	**<0.0001**	1.04(0.96-1.14)	0.335
Death within 90 days	1.07 (0.99-1.16)	0.092	1.23(1.14-1.32)	**<0.0001**
Any serious adverse event within 90 days	1.05 (1.00-1.11)	0.057	1.07(1.01-1.13)	**0.021**
	Variability SD of SBP 1-24 hours		**Variability** SD of SBP 1-24 hours	
Favorable shift on the mRS score at 90 days	0.88 (0.81-0.96)	**0.004**	0.84(0.76-0.93)	**0.001**
MRS score 0-1 at 90 days	0.91 (0.82-1.02)	0.103	0.87(0.77-0.99)	**0.035**
MRS score 0-2 at 90 days	0.85 (0.76-0.95)	**0.004**	0.81(0.71-0.92)	**0.001**
Any intracranial hemorrhage within 7 days	1.22 (1.08-1.37)	**0.002**	1.22(1.06-1.41)	**0.007**
Death or neurologic deterioration§ within 7 days	1.35 (1.18-1.54)	**<0.0001**	1.48(1.23-1.79)	**<0.0001**
Death within 90 days	1.32 (1.13-1.55)	**0.001**	1.32(1.12-1.55)	**0.001**
Any serious adverse event within 90 days	1.37 (1.23-1.54)	**<0.0001**	1.35(1.18-1.54)	**<0.0001**
	Magnitude baseline-minimum ≤1 hr		**Magnitude** baseline-minimum ≤24 hr	
Favorable shift on the mRS score at 90 days	1.00 (0.97-1.04)	0.969	1.03 (0.99-1.08)	0.117
MRS score 0-1 at 90 days	1.01 (0.96-1.05)	0.823	1.04 (0.98-1.09)	0.176
MRS score 0-2 at 90 days	0.99 (0.94-1.03)	0.542	1.04 (0.99-1.10)	0.124
Any intracranial hemorrhage within 7 days	1.01 (0.96-1.06)	0.685	1.00 (0.94-1.06)	0.936
Death or neurologic deterioration§ within 7 days	1.06 (1.00-1.12)	**0.041**	0.91 (0.84-0.99)	**0.029**
Death within 90 days	0.98 (0.91-1.05)	0.500	1.01 (0.95-1.09)	0.683
Any serious adverse event within 90 days	1.00 (0.95-1.04)	0.877	1.02 (0.96-1.07)	0.578

SBP denotes systolic blood pressure; OR, odds ratio; CI, confidence interval; mRS, modified Rankin scale (scores are 0 = no symptoms, 1 = symptoms without disability, 2 = disability but independent function, 3 = disability with some assistance, 4 = disability with moderate assistance, 5 = bedridden, full dependency, and 6 = death); SD, standard deviation.

†OR per 10 mmHg increase in SBP summary measure, adjusted for age, sex, Asian vs. non-Asian, degree of neurological impairment (NIHSS score), pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

§Neurologic deterioration defined as an increase of ≥4 points on the NIHSS or a decline of ≥2 on the Glasgow Coma Scale within 24 hr post-randomization.

SUPPLEMENTAL MATERIAL

Associations of early systolic blood pressure control and outcome after thrombolysis-eligible acute ischemic stroke: results from the ENhanced Control of Hypertension ANd Thrombolysis stroke study (ENCHANTED)

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Supplemental File

Table SI Associations of categorical BP parameters (attained and variability of 1-24h, and magnitude in 1 hour) on outcomes

		Events (n,%)	OR (95%CI) *	P trend
Favorable shift on the mRS scores at 90 days				
Attained SBP	<110 mmHg		0.75(0.51-1.1)	
	110-120 mmHg		1.0	0.006
	120-130 mmHg		0.82(0.64-1.04)	
	130–140 mmHg		0.68(0.54-0.86)	
	140–150 mmHg		0.54(0.43-0.69)	
	150–160 mmHg		0.44(0.34-0.57)	
	160–170 mmHg		0.39(0.29-0.53)	
	≥170 mmHg		0.31(0.20-0.46)	
SBP variability	<5 mmHg		1.0	<0.0001
	5-10 mmHg		1.32(1.10-1.60)	
	10-15 mmHg		1.02(0.84-1.23)	
	15-20 mmHg		1.13(0.91-1.39)	
	20-25 mmHg		1.06(0.81-1.38)	
	≥25 mmHg		0.77(0.56-1.05)	
Magnitude of SBP reduction	<0 mmHg		1.14(0.94-1.38)	0.617
	0-10 mmHg		1.0	
	10-20 mmHg		1.01(0.86-1.18)	
	20-30 mmHg		0.97(0.82-1.15)	
	30-40 mmHg		0.93(0.76-1.14)	
	40-50 mmHg		1.17(0.90-1.51)	
	≥50 mmHg		1.00(0.73-1.37)	
MRS scores 0-1 at 90 days				
Attained SBP	<110 mmHg	62/ 115 (53.9)	0.79(0.49-1.28)	0.004
	110-120 mmHg	196/ 323 (60.7)	1.0	
	120-130 mmHg	431/ 749 (57.5)	0.82(0.60-1.11)	
	130–140 mmHg	605/1137 (53.2)	0.64(0.47-0.85)	
	140–150 mmHg	527/1066 (49.4)	0.54(0.40-0.73)	
	150–160 mmHg	274/ 661 (41.5)	0.40(0.29-0.55)	
	160–170 mmHg	92/ 278 (33.1)	0.30(0.20-0.45)	
	≥170 mmHg	31/ 102 (30.4)	0.27(0.16-0.47)	
SBP variability	<5 mmHg	242/ 475 (50.9)	1.0	0.007
	5-10 mmHg	797/1435 (55.5)	1.32(1.04-1.67)	
	10-15 mmHg	656/1334 (49.2)	1.02(0.81-1.30)	
	15-20 mmHg	339/ 707 (47.9)	1.16(0.89-1.52)	
	20-25 mmHg	121/ 288 (42.0)	1.02(0.73-1.44)	
	≥25 mmHg	63/ 192 (32.8)	0.80(0.54-1.20)	
Magnitude of SBP reduction	<0 mmHg	254/ 573 (44.3)	1.07(0.84-1.36)	0.953
	0-10 mmHg	457/ 955 (47.9)	1.0	
	10-20 mmHg	556/1099 (50.6)	0.98(0.81-1.19)	
	20-30 mmHg	474/ 903 (52.5)	0.92(0.75-1.13)	
	30-40 mmHg	265/ 497 (53.3)	0.92(0.72-1.19)	
	40-50 mmHg	139/ 250 (55.6)	1.18(0.85-1.64)	
	≥50 mmHg	73/ 154 (47.4)	0.98(0.66-1.45)	
MRS score 0-2 at 90 days				
Attained SBP	<110 mmHg	80/ 115 (69.6)	0.83(0.49-1.41)	0.019
	110-120 mmHg	239/ 323 (74.0)	1.0	
	120-130 mmHg	520/ 749 (69.4)	0.77(0.55-1.08)	
	130–140 mmHg	787/1137 (69.2)	0.78(0.57-1.09)	
	140–150 mmHg	676/1066 (63.4)	0.57(0.41-0.80)	
	150–160 mmHg	372/ 661 (56.3)	0.44(0.31-0.63)	
	160–170 mmHg	134/ 278 (48.2)	0.34(0.23-0.51)	
	≥170 mmHg	49/ 102 (48.0)	0.35(0.20-0.60)	
SBP variability	<5 mmHg	309/ 475 (65.1)	1.0	<0.0001
	5-10 mmHg	995/1435 (69.3)	1.34(1.04-1.72)	
	10-15 mmHg	867/1334 (65.0)	1.10(0.85-1.41)	
	15-20 mmHg	446/ 707 (63.1)	1.22(0.92-1.61)	
	20-25 mmHg	155/ 288 (53.8)	0.86(0.61-1.22)	
	≥25 mmHg	85/ 192 (44.3)	0.66(0.44-0.99)	
Magnitude of SBP reduction	<0 mmHg	347/ 573 (60.6)	1.14(0.89-1.46)	
	0-10 mmHg	602/ 955 (63.0)	1.0	
	10-20 mmHg	711/1099 (64.7)	0.93(0.75-1.15)	

	20-30 mmHg	604/ 903 (66.9)	0.87(0.69-1.09)	
	30-40 mmHg	332/ 497 (66.8)	0.85(0.64-1.11)	
	40-50 mmHg	167/ 250 (66.8)	1.02(0.71-1.45)	
	≥50 mmHg	94/ 154 (61.0)	0.95(0.63-1.43)	
Any intracranial hemorrhage within 7 days				
Attained SBP	<110 mmHg	22/ 119 (18.5)	0.75(0.43-1.3)	0.064
	110-120 mmHg	75/ 336 (22.3)	1.0	
	120-130 mmHg	121/ 761 (15.9)	0.62(0.44-0.88)	
	130–140 mmHg	183/1151 (15.9)	0.67(0.48-0.93)	
	140–150 mmHg	216/1087 (19.9)	0.86(0.61-1.20)	
	150–160 mmHg	126/ 669 (18.8)	0.70(0.49-1.01)	
	160–170 mmHg	68/ 284 (23.9)	0.94(0.62-1.42)	
	≥170 mmHg	25/ 104 (24.0)	0.89(0.50-1.58)	
SBP variability	<5 mmHg	72/ 481 (15.0)	1.0	0.563
	5-10 mmHg	241/1459 (16.5)	1.10(0.81-1.48)	
	10-15 mmHg	265/1359 (19.5)	1.35(1.00-1.83)	
	15-20 mmHg	144/ 725 (19.9)	1.32(0.95-1.84)	
	20-25 mmHg	59/ 294 (20.1)	1.13(0.75-1.70)	
	≥25 mmHg	55/ 193 (28.5)	2.00(1.29-3.10)	
Magnitude of SBP reduction	<0 mmHg	121/ 589 (20.5)	0.85(0.65-1.12)	0.275
	0-10 mmHg	195/ 974 (20.0)	1.0	
	10-20 mmHg	213/1118 (19.1)	1.05(0.83-1.32)	
	20-30 mmHg	151/ 915 (16.5)	0.97(0.75-1.25)	
	30-40 mmHg	76/ 504 (15.1)	0.93(0.68-1.27)	
	40-50 mmHg	42/ 254 (16.5)	0.93(0.62-1.39)	
	≥50 mmHg	38/ 157 (24.2)	1.19(0.77-1.84)	
Death within 90 days				
Attained SBP	<110 mmHg	13/ 119 (10.9)	1.96(0.89-4.33)	0.905
	110-120 mmHg	21/ 336 (6.3)	1.0	
	120-130 mmHg	49/ 761 (6.4)	0.90(0.51-1.58)	
	130–140 mmHg	84/1151 (7.3)	0.91(0.53-1.57)	
	140–150 mmHg	99/1087 (9.1)	1.20(0.69-2.06)	
	150–160 mmHg	85/ 669 (12.7)	1.52(0.87-2.66)	
	160–170 mmHg	33/ 284 (11.6)	1.19(0.63-2.27)	
	≥170 mmHg	17/ 104 (16.3)	1.72(0.79-3.77)	
SBP variability	<5 mmHg	44/ 481 (9.1)	1.0	<0.0001
	5-10 mmHg	94/1459 (6.4)	0.61(0.41-0.92)	
	10-15 mmHg	120/1359 (8.8)	0.89(0.60-1.32)	
	15-20 mmHg	69/ 725 (9.5)	0.76(0.49-1.19)	
	20-25 mmHg	33/ 294 (11.2)	0.77(0.45-1.32)	
	≥25 mmHg	41/ 193 (21.2)	1.72(1.01-2.93)	
Magnitude of SBP reduction	<0 mmHg	69/ 589 (11.7)	1.11(0.76-1.61)	0.506
	0-10 mmHg	84/ 974 (8.6)	1.0	
	10-20 mmHg	99/1118 (8.9)	1.11(0.79-1.56)	
	20-30 mmHg	66/ 915 (7.2)	1.03(0.71-1.5)	
	30-40 mmHg	41/ 504 (8.1)	1.23(0.79-1.91)	
	40-50 mmHg	26/ 254 (10.2)	1.18(0.7-2.01)	
	≥50 mmHg	16/ 157 (10.2)	0.89(0.47-1.69)	
Death or neurologic deterioration§ within 7 days				
Attained SBP	<110 mmHg	12/ 119 (10.1)	1.56(0.74-3.28)	0.064
	110-120 mmHg	23/ 336 (6.8)	1.0	
	120-130 mmHg	65/ 761 (8.5)	1.17(0.71-1.94)	
	130–140 mmHg	117/1151 (10.2)	1.32(0.82-2.14)	
	140–150 mmHg	152/1087 (14.0)	1.96(1.21-3.17)	
	150–160 mmHg	105/ 669 (15.7)	2.27(1.38-3.74)	
	160–170 mmHg	56/ 284 (19.7)	3.00(1.74-5.17)	
	≥170 mmHg	27/ 104 (26.0)	4.05(2.11-7.77)	
SBP variability	<5 mmHg	59/ 481 (12.3)	1.0	<0.0001
	5-10 mmHg	147/1459 (10.1)	0.78(0.56-1.09)	
	10-15 mmHg	165/1359 (12.1)	0.97(0.70-1.34)	
	15-20 mmHg	90/ 725 (12.4)	0.93(0.64-1.33)	
	20-25 mmHg	44/ 294 (15.0)	1.11(0.72-1.73)	
	≥25 mmHg	52/ 193 (26.9)	2.06(1.31-3.23)	
Magnitude of SBP reduction	<0 mmHg	78/ 589 (13.2)	1.00(0.72-1.38)	0.137
	0-10 mmHg	115/ 974 (11.8)	1.0	
	10-20 mmHg	132/1118 (11.8)	1.09(0.83-1.44)	

	20-30 mmHg	99/ 915 (10.8)	1.05(0.78-1.42)	
	30-40 mmHg	66/ 504 (13.1)	1.39(0.98-1.96)	
	40-50 mmHg	41/ 254 (16.1)	1.62(1.07-2.44)	
	≥50 mmHg	26/ 157 (16.6)	1.51(0.92-2.47)	
Any serious adverse event within 90 days				
Attained SBP	<110 mmHg	29/ 119 (24.4)	1.10(0.65-1.86)	0.305
	110-120 mmHg	80/ 336 (23.8)	1.0	
	120-130 mmHg	155/ 761 (20.4)	0.73(0.52-1.02)	
	130–140 mmHg	229/1151 (19.9)	0.72(0.52-1.00)	
	140–150 mmHg	276/1087 (25.4)	0.97(0.70-1.34)	
	150–160 mmHg	192/ 669 (28.7)	0.97(0.69-1.38)	
	160–170 mmHg	95/ 284 (33.5)	1.04(0.69-1.55)	
	≥170 mmHg	39/ 104 (37.5)	1.08(0.63-1.85)	
SBP variability	<5 mmHg	88/ 481 (18.3)	1.0	0.014
	5-10 mmHg	273/1459 (18.7)	0.93(0.70-1.24)	
	10-15 mmHg	332/1359 (24.4)	1.29(0.97-1.71)	
	15-20 mmHg	211/ 725 (29.1)	1.35(0.99-1.85)	
	20-25 mmHg	99/ 294 (33.7)	1.37(0.95-1.99)	
	≥25 mmHg	92/ 193 (47.7)	2.42(1.61-3.65)	
Magnitude of SBP reduction	<0 mmHg	171/ 589 (29.0)	0.93(0.72-1.20)	0.770
	0-10 mmHg	249/ 974 (25.6)	1.0	
	10-20 mmHg	269/1118 (24.1)	1.02(0.82-1.27)	
	20-30 mmHg	200/ 915 (21.9)	1.02(0.80-1.29)	
	30-40 mmHg	100/ 504 (19.8)	0.96(0.72-1.29)	
	40-50 mmHg	59/ 254 (23.2)	0.95(0.66-1.37)	
	≥50 mmHg	47/ 157 (29.9)	1.04(0.68-1.58)	

SBP denotes systolic blood pressure, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, SAE serious adverse events

*model was adjusted for age, sex, Asian vs. non-Asian, degree of neurological impairment (NIHSS score), pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

Table SII Associations of continuous BP parameters on the outcomes using complete data

	Model 1*		Model 2†	
	OR (95%CI)	P value	OR (95%CI)	P value
Favorable shift on the ordinal mRS				
Attained SBP	0.85(0.82-0.88)	<0.0001	0.84(0.80-0.87)	<0.0001
SBP variability	0.76(0.7-0.83)	<0.0001	0.87(0.80-0.95)	0.0002
Magnitude of SBP reduction	1.03(1-1.06)	0.0519	1.00(0.97-1.03)	0.9718
MRS 0-1				
Attained SBP	0.84(0.8-0.87)	<0.0001	0.81(0.77-0.85)	<0.0001
SBP variability	0.79(0.72-0.87)	<0.0001	0.90(0.81-1.00)	0.0594
Magnitude of SBP reduction	1.04(1.01-1.08)	0.022	1.01(0.96-1.05)	0.759
MRS 0-2				
Attained SBP	0.85(0.81-0.88)	<0.0001	0.83(0.79-0.88)	<0.0001
SBP variability	0.75(0.68-0.83)	<0.0001	0.84(0.75-0.94)	0.002
Magnitude of SBP reduction	1.02(0.98-1.06)	0.326	0.99(0.94-1.03)	0.528
Any adjudicated ICH				
Attained SBP	1.03(0.98-1.09)	0.21	1.03(0.98-1.10)	0.264
SBP variability	1.28(1.14-1.43)	<0.0001	1.22(1.08-1.38)	0.002
Magnitude of SBP reduction	0.96(0.92-1.01)	0.08	1.00(0.95-1.05)	0.909
Death				
Attained SBP	1.12(1.05-1.21)	0.001	1.07(0.98-1.16)	0.115
SBP variability	1.60(1.39-1.84)	<0.0001	1.41(1.20-1.65)	<0.0001
Magnitude of SBP reduction	0.98(0.92-1.04)	0.551	0.98(0.91-1.05)	0.531
Death or neurologic deterioration in the first 7 d				
Attained SBP	1.24(1.17-1.32)	<0.0001	1.24(1.16-1.33)	<0.0001
SBP variability	1.38(1.21-1.57)	<0.0001	1.38(1.21-1.58)	<0.0001
Magnitude of SBP reduction	1.06(1-1.11)	0.035	1.06(1.00-1.12)	0.055
Any SAE				
Attained SBP	1.09(1.04-1.14)	0.0007	1.05(0.99-1.11)	0.080
SBP variability	1.7(1.53-1.89)	<0.0001	1.39(1.24-1.56)	<0.0001
Magnitude of SBP reduction	0.97(0.93-1.01)	0.105	0.99(0.94-1.03)	0.590

SBP denotes systolic blood pressure, NIHSS National Institutes of Health Stroke Scale, mRS, modified Rankin scale

*Model with attained BP (continuous), BP variability (continuous), and magnitude of reduction (continuous); OR was for per 10 mmHg increase

†Model 1 + age, sex, Asian vs. non-Asian, degree of neurological impairment (NIHSS score), pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

Table SIII Associations of continuous BP parameters (day 2-7) on the outcomes using complete data

	Model 1*		Model 2†	
	OR (95%CI)	P value	OR (95%CI)	P value
Favorable shift on the ordinal mRS				
Attained SBP	0.93(0.9-0.97)	0.0007	0.87(0.83-0.92)	<0.0001
SBP variability	0.48(0.42-0.53)	<0.0001	0.64(0.57-0.73)	<0.0001
Magnitude of SBP reduction	1.05(1.01-1.08)	0.006	0.98(0.94-1.02)	0.406
MRS 0-1				
Attained SBP	0.92(0.88-0.96)	0.0002	0.82(0.77-0.88)	<0.0001
SBP variability	0.53(0.47-0.61)	<0.0001	0.73(0.63-0.86)	0.0001
Magnitude of SBP reduction	1.04(1.01-1.08)	0.0202	0.96(0.92-1.01)	0.146
MRS 0-2				
Attained SBP	0.92(0.88-0.97)	0.0011	0.87(0.82-0.93)	0.0001
SBP variability	0.49(0.43-0.56)	<0.0001	0.63(0.53-0.74)	<0.0001
Magnitude of SBP reduction	1.05(1.01-1.09)	0.0226	0.99(0.94-1.04)	0.709
Any adjudicated ICH				
Attained SBP	0.96(0.9-1.01)	0.1248	1.01(0.94-1.09)	0.755
SBP variability	1.44(1.24-1.68)	<0.0001	1.16(0.97-1.38)	0.103
Magnitude of SBP reduction	0.98(0.93-1.02)	0.2853	1.04(0.99-1.11)	0.147
Death				
Attained SBP	0.98(0.9-1.07)	0.6856	0.91(0.82-1.02)	0.0933
SBP variability	2.91(2.38-3.56)	<0.0001	2.72(2.15-3.44)	<0.0001
Magnitude of SBP reduction	0.93(0.87-0.99)	0.0264	0.88(0.81-0.96)	0.006
Death or neurologic deterioration in the first 7 d				
Attained SBP	1.19(1.1-1.28)	<0.0001	1.19(1.09-1.29)	0.0001
SBP variability	1.77(1.48-2.11)	<0.0001	1.72(1.42-2.09)	<0.0001
Magnitude of SBP reduction	1.07(1.01-1.13)	0.0269	1.06(0.99-1.14)	0.106
Any SAE				
Attained SBP	1.04(0.98-1.09)	0.196	1.09(1.02-1.16)	0.016
SBP variability	1.96(1.69-2.26)	<0.0001	1.34(1.14-1.58)	0.0004
Magnitude of SBP reduction	0.97(0.93-1.01)	0.185	1.05(0.99-1.11)	0.082

SBP denotes systolic blood pressure, NIHSS National Institutes of Health Stroke Scale, mRS, modified Rankin scale, SAE serious adverse events

*Model was with attained BP (continuous), BP variability (continuous), and magnitude of reduction (continuous); OR was for per 10 mmHg increase

†Model 1 + age, sex, Asian vs. non-Asian, degree of neurological impairment (NIHSS score), pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

Table SIV Test modification for the association of continuous BP parameters on favorable shift on the ordinal mRS scores at 90 days

Subgroup		P interaction
Sex	Female	0.271
	Male	
Age	<65	0.448
	≥65	
Ethnicity	Asian	0.175
	Non-Asians	
NIHSS	<10	0.358
	≥10	
Onset to treatment	<3	0.708
	≥3	
Baseline SBP	<150	0.275
	≥150	
History of hypertension	Yes	0.007
	No	
Currently treated hypertension	Yes	0.050
	No	
Antiplatelet agent use	Yes	0.177
	No	
History of atrial fibrillation	Yes	0.300
	No	
Final diagnosis of ischemic stroke	Large artery atheroma	0.657
	Small vessel disease	
	Cardioembolic	
	Other definite or uncertain pathology	

NIHSS: National Institutes of Health Stroke Scale; SBP systolic blood pressure

Table SV Associations of continuous BP parameters on favorable shift on ordinal mRS score at 90 days by history of hypertension

		Mean (SD)	OR (95%CI)	P value
History of hypertension				
No (n=1592)	Attained SBP	134 (15.1)	0.91(0.85-0.97)	0.005
	SBP variability	12 (6.3)	0.78(0.67-0.90)	0.001
	Magnitude of SBP reduction	15 (16.3)	1.09(1.02-1.16)	0.007
Yes (n=2916)	Attained SBP	142 (14.5)	0.81(0.77-0.85)	<0.0001
	SBP variability	12 (6.5)	0.94(0.84-1.04)	0.214
	Magnitude of SBP reduction	17 (17.2)	0.96(0.92-1.00)	0.073

Adjusted for age, sex, Asian vs. non-Asian, degree of neurological impairment (NIHSS score), pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin] and antihypertensive agents, and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase)

Table SVI Relative influence of three SBP summary measures on the outcomes, adjusting for baseline characteristics

Variables	Outcomes (%)				
	Ordinal mRS	Any ICH	Death	Death or neurological deterioration within the first 7 days	Any SAE
Attained SBP, 1-24 hour	12.74	16.39	13.13	15.14	15.14
Variability of SBP, 1-24 hour	14.66	18.97	14.62	18.73	18.73
Magnitude of reduction of SBP in the first hour	13.66	19.26	17.30	16.69	16.68
Age	15.08	20.09	15.36	16.30	16.30
Sex	0.68	1.00	0.78	0.92	0.92
Ethnicity (Asian vs. non-Asian)	0.65	0.84	0.65	0.93	0.93
NIHSS score	11.81	12.37	15.17	8.26	8.26
Pre-morbid function [mRS scores 0 or 1])	25.75	3.83	16.55	17.26	17.26
History of stroke	0.55	0.64	0.52	0.61	0.61
Coronary artery disease	0.69	0.87	1.01	0.52	0.52
Diabetes mellitus	0.71	0.90	0.77	0.88	0.88
Atrial fibrillation	0.95	1.64	1.66	0.91	0.91
Pre-morbid use of antithrombotic agents	1.56	2.61	1.92	2.08	2.08
Randomized treatment (intensive vs. guideline BP lowering treatment)	0.51	0.58	0.57	0.77	0.77

Boosting algorithm was used to find out the relative influence across all the covariates.
The relative influence is an empirical calculation based on the number of times one variable entered into a tree to explain the outcome. The higher the number is, the more important of the variable for the outcome.

SBP denotes systolic blood pressure, ICH intracerebral hemorrhage, mRS modified Rankin scale

Figure SI Flow chart of the included patients

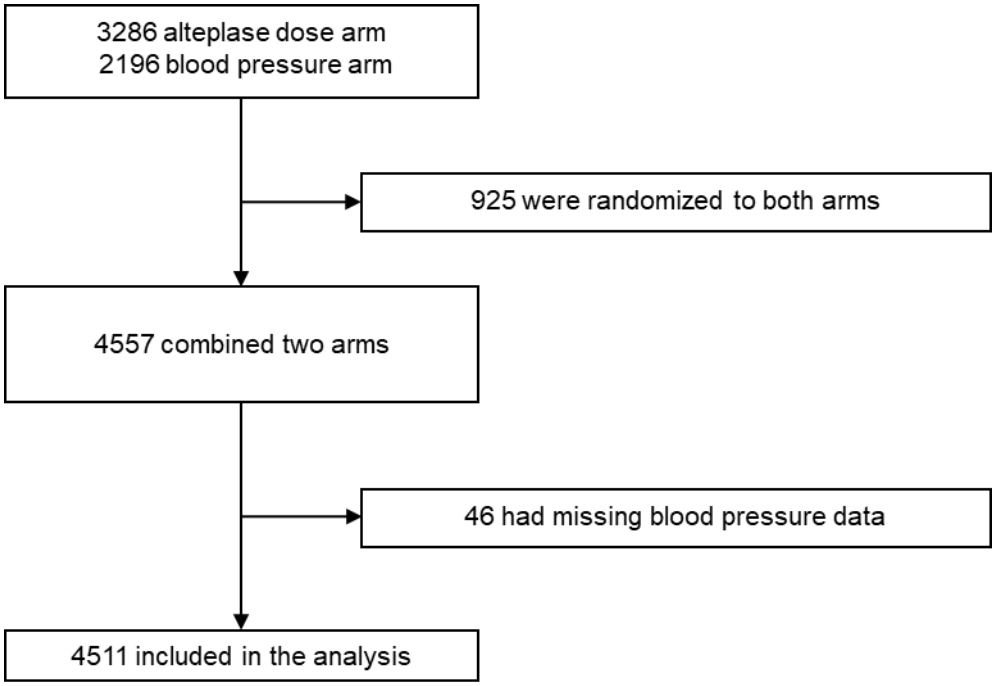
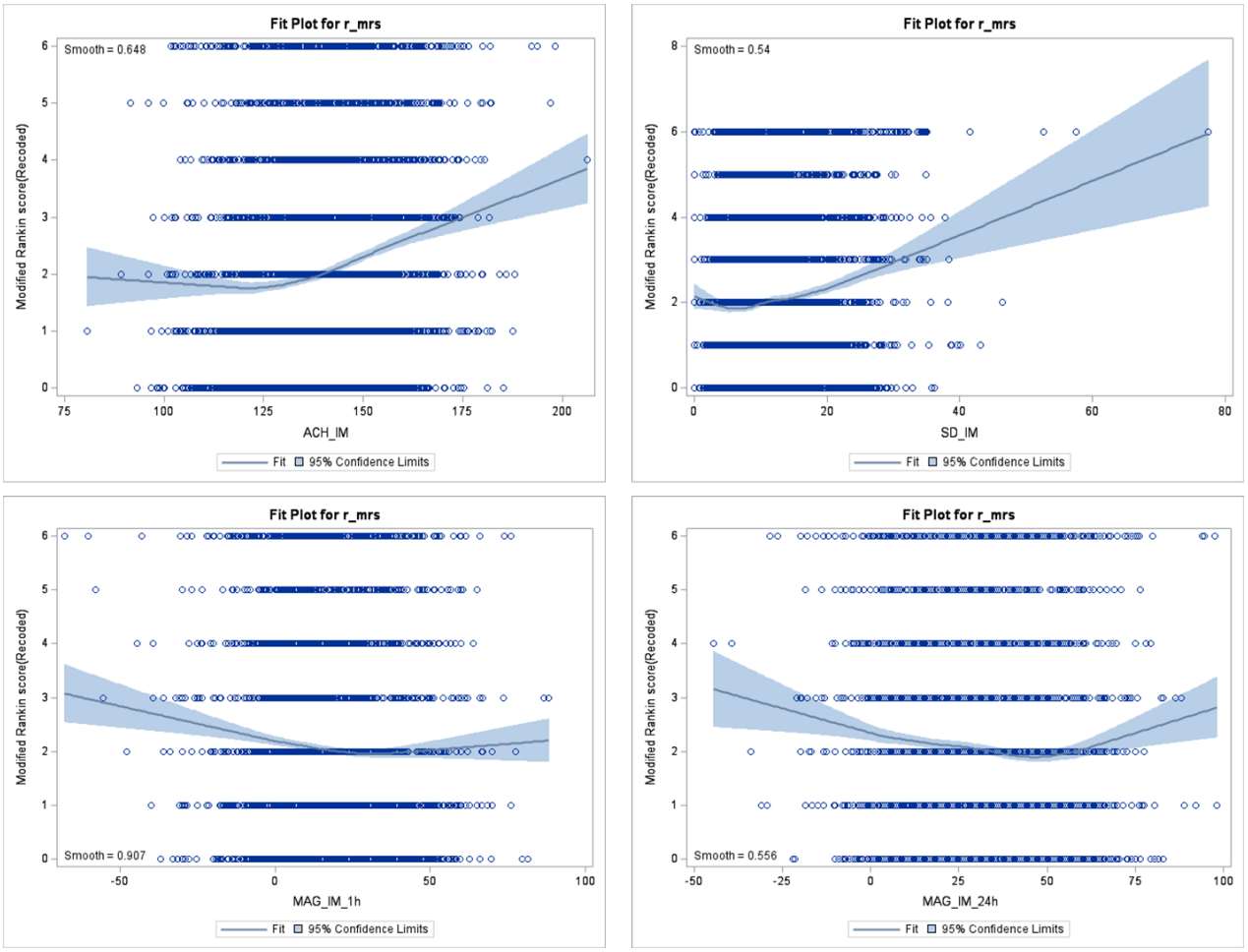
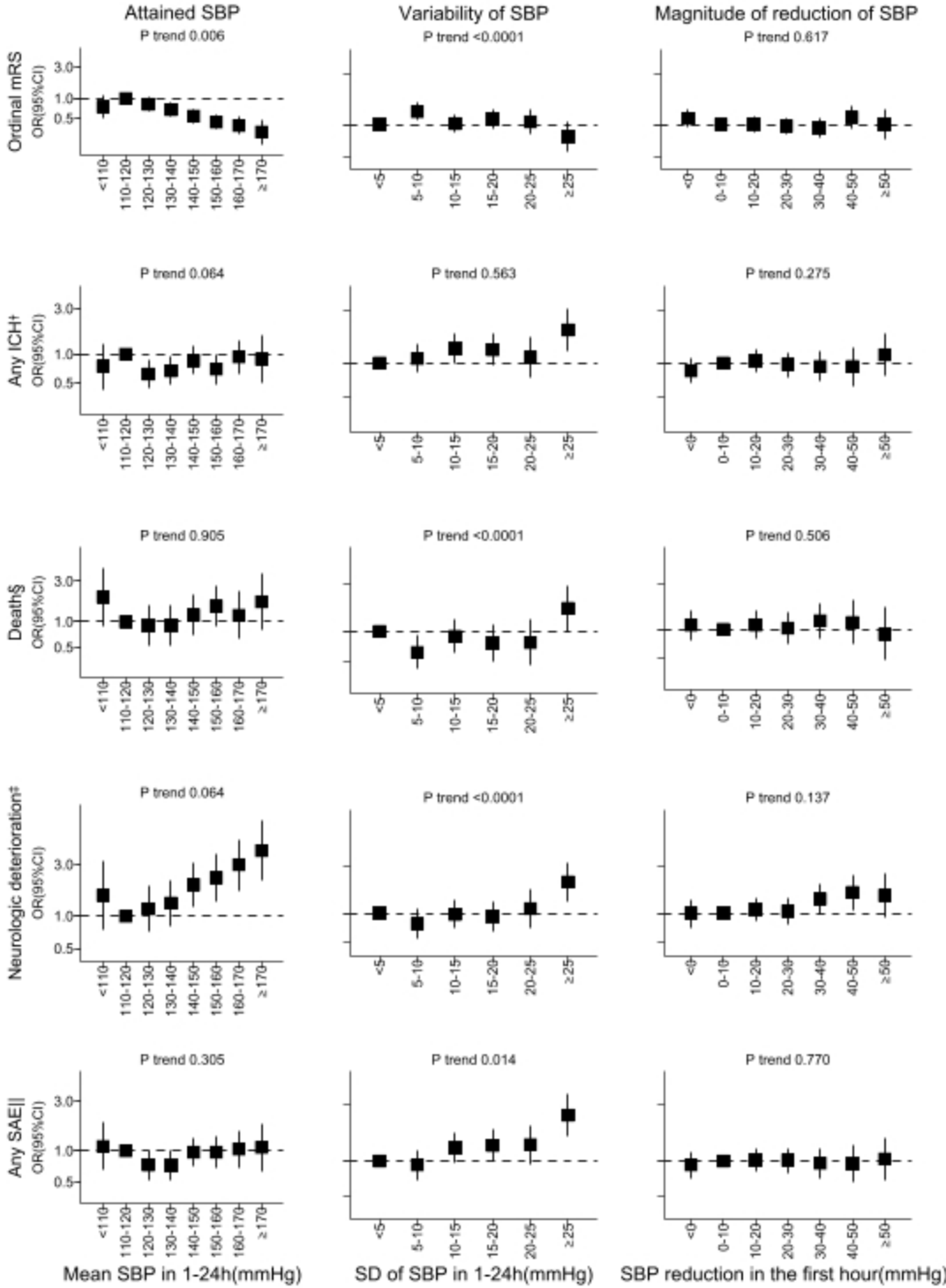


Figure SII LOESS plot for associations between blood pressure control parameters and ordinal modified Rankin scale scores




Attained SBP
Variability of SBP
Magnitude of reduction of SBP
Ordinal mRS
Any ICH†
Death§
Neurologic deterioration‡
Any SAE||
OR(95%CI)
P trend 0.006
P trend <0.0001
P trend 0.617
P trend 0.064
P trend 0.563
P trend 0.275
P trend 0.905
P trend <0.0001
P trend 0.506
P trend 0.064
P trend <0.0001
P trend 0.137
P trend 0.305
P trend 0.014
P trend 0.770
3.0
1.0
0.5
<110
110-120
120-130
130-140
140-150
150-160
160-170
≥170
<5
5-10
10-15
15-20
20-25
≥25
<0
0-10
10-20
20-30
30-40
40-50
≥50
Mean SBP in 1-24h(mmHg)
SD of SBP in 1-24h(mmHg)
SBP reduction in the first hour(mmHg)†